

Subependymoma revisited: clinicopathological evaluation of 83 cases

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Abstract

Object Subependymomas are rare ependymal neoplasms. To date, a large clinicopathologic study of these benign neoplasms treated with modern neurosurgical techniques has not been reported.

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Methods Eighty-three cases of subependymoma were retrieved from the files of the Armed Forces Institute of Pathology. Clinicopathological features were reviewed; chromogenic in situ hybridization analysis for chromosome 22 was performed ($n = 8$), and patient follow-up was obtained ($n = 34$). Overall, the patients included 68 males and 15 females, 1.5 to 85 years of age (mean, 51.0 years). Twenty-seven cases were discovered at autopsy and the remaining were surgical specimens ($n = 56$). Tumors arose in the posterior fossa ($n = 43$), lateral ventricles ($n = 37$), spinal cord (2) and only one arose in the temporal horn. Tumors ranged in size from 2.0 mm to 60 mm in greatest dimension (mean, 23.0 mm). Eighteen-percent (15/83) of subependymomas exhibited a mixed histologic pattern; that is, subependymoma together with another glial tumor. The most common mixture (13/15) was subependymoma and ependymoma. Surgical excision was used in all symptomatic patients; 10 patients received radiation. Four patients developed a recurrence due to incomplete excision. All patients were without evidence of disease at the last follow-up: alive ($n = 28$) or dead ($n = 8$).

Conclusions Age is the only variable found to be significantly associated with survival. Currently, surgical methods result in an excellent long-term clinical outcome. Subependymomas do not appear to be associated with NF2 mutations.

Keywords Central nervous system · CISH · CT · Ependymoma · MRI · Subependymoma

Introduction

Subependymomas have stirred little interest in the past and have been largely ignored in the literature. This continued

neglect is not surprising, considering that they reside at the benign end of the biological spectrum, represent only 0.2 to 0.7% of intracranial tumors and are often clinically silent [1, 12, 16, 17, 23]. They generally arise from the floor of the fourth ventricle; sometimes, masses present in the supratentorial compartment near the foramen of Monro, or exceptionally, in relation to the central canal of the spinal cord or other intraventricular sites [1, 2, 10, 11, 23, 24, 26]. Rarely, extraventricular sites have been reported [5]. Subependymomas can become symptomatic at any age, but exhibit a peak incidence in middle-aged and elderly patients [19, 26]. Information as to gender predilection varies little; most reviewers describe a higher incidence in men than in women [16, 23, 26]. One study that analyzed seven cases of symptomatic supratentorial subependymomas found a ratio of 5:2 females to males [8]. Symptoms depend on the location and size of the tumor, but the clinical presentation is often non-specific [1, 19, 25]. Most symptomatic patients (80%) present with symptoms related to hydrocephalus as a consequence of ventricular obstruction. Less commonly, focal neurologic deficits, seizures, and subarachnoid hemorrhage have been reported [1, 19, 25]. Nearly all cases are effectively treated by surgical excision, and recurrence is rare, usually related to incomplete excision [9, 19, 25].

Subependymoma was initially recognized as a distinct pathologic entity by Scheinker in 1945 [22]. In 1978, Scheithauer reviewed a total of 95 cases from the literature, the largest study to date, including 21 symptomatic cases from his personal files [23]. However, since the majority of these cases were operated on before the advent of modern microneurosurgical techniques, they were associated with high mortality rates. In recent years, only small series and isolated case reports have appeared in the literature.

The purpose of the current study was to re-evaluate the clinicopathological features in a large cohort to further define the natural history of subependymoma in response to modern intervention. In addition, given that little is known about their molecular attributes, we investigated representative tumors for NF2 deletions using an NF2 deletion probe for chromogenic in situ hybridization (CISH).

Materials and methods

Patient population

The cases were retrieved from the files of the Neuropathologic Tumor Registry of the Armed Forces Institute of Pathology, Washington, DC, between 1970 and 1999. During that period, 93 cases were coded as subependymoma,

but sufficient material was available for study in 83 cases. Materials within the Institute's files (radiographic, surgical pathology, and operative reports) were reviewed for patient demographics (gender, age); symptoms and physical findings, duration at presentation and past medical and surgical history. Complete follow-up data, available for 34 patients, included information regarding tumor location, presence of recurrent disease, treatment modalities used and current patient status. Extent of resection was defined as subtotal resection (STR) or gross total resection (GTR) based on information coded at the treating institution. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

Pathological/chromogenic in situ hybridization analysis

The macroscopic pathology noted within this study was gathered from gross descriptions of the neoplasms given by contributing pathologists and neurosurgeons, and included the exact tumor location, lateralization and tumor size (greatest dimension in millimeters). All histopathologic specimens ($n = 83$) were examined by two neuropathologists (EJR and MS). Hematoxylin and eosin-stained slides from all cases and immunohistochemical preparations available in selected cases (glial fibrillary acidic protein-GFAP, Ki-67) were reviewed, with the presence or absence of specific histologic features tabulated as follows: cyst formation, calcification, pleomorphism, vascular hyalinization, necrosis, mixed histologic pattern, and for those with a mixed histology, the character of the transition (abrupt or indistinct), and mitotic figures (number of mitotic figures per 10 high power fields [magnification at 40 \times with a 10 \times objective lens using an Olympus BX40 microscope]).

Chromogenic in situ hybridization (CISH) for the NF2 deletion was performed on 8 cases according to the manufacturer's (Zymed Laboratories Inc, South San Francisco, CA, USA) instructions on 5 mm thick unstained sections from archival formalin-fixed, paraffin-embedded tumor samples. The slides were deparaffinized in xylene and graded alcohol solutions. Heat pretreatment was carried out in the pretreatment buffer (Zymed Laboratories, Inc.) at 98–100 $^{\circ}$ C for 15 min. The tissue was digested with the Zymed FFPE digestion enzyme for 10 min. The slides were washed with PBS and dehydrated with graded alcohols. The ready-to-use Zymed SpotLightTM digoxigenin-labeled NF2 deletion probe was applied to the slides, which were covered by CISHTM UnderCover Slips (Zymed).

Radiographic studies

The preoperative magnetic imaging (MR) and computerized tomography (CT) findings were correlated with the pathology in 22 cases of subependymoma, including 16 CT and 12 MR studies. Imaging studies were obtained over time using a variety of CT and MR scanners, and were reviewed by two radiologists, including a senior neuroradiologist. Neoplasm features assessed on neuroimaging studies (either CT or MR) were as follows: location, shape, presence and degree of hydrocephalus, presence and degree of edema, cystic changes and transependymal extension when present.

CT images were evaluated for the presence of calcification or hemorrhage, predominant attenuation related to gray matter and homogeneity of the solid component. In 9 cases in which images were obtained both before (non-contrast CT, NCCT) and after the administration of intravenous contrast material (enhanced-contrast CT, ECCT) were available, they were assessed for degree and pattern of enhancement.

MR images were evaluated for the predominant signal intensity and homogeneity of the tumor on T1w and T2w images. MR images obtained after intravenous gadolinium chelate injection were evaluated for the degree and predominant pattern of contrast enhancement.

Statistical methods

Survival curves and five-year survival percentages were estimated using the Kaplan–Meier method, and were compared using the log rank test. *P* values < 0.05 were considered statistically significant. STATA (version 8.0; Stat Corp, College Station, TX) software was used to analyze post-operative survival data.

Results

Patient characteristics

The overall study group consisted of 68 males and 15 females (4.5:1) ranging in age from 1.5 years to 85 years, with an overall mean age at presentation of 50.0 years (median, 55 years). The average age at presentation for males was older than females, at 57 and 43.0 years, respectively. There were 54 Caucasians, 5 African Americans and 2 were listed as Mongolian; 22 patients had an unknown ethnic background. Twenty-seven tumors were not detected until autopsy in patients who died from unrelated causes.

There was a wide range of clinical presentations within the cohort with up to 5 presenting symptoms recorded for

each patient. The most common presenting symptoms were headaches (34 cases), gait problems (13 cases), ataxia (13 cases), nausea (8 cases), dizziness (7 cases) and vomiting (7 cases). Duration of symptoms ranged from 3 days in a patient described as having apathy to 15 years in a patient carrying a diagnosis of schizophrenia. For the most part, symptomatic cases were correlated with the size of the neoplasm. It is noteworthy that one patient in our series carried a diagnosis of neurofibromatosis (NF1).

Tumor localization and size

Patients most frequently presented with a mass lesion in the fourth ventricle (43/83) followed by the lateral ventricle (36/83); 2 tumors were identified in the intramedullary compartment of the spinal cord and a single tumor presented in the temporal horn of the lateral ventricle. Forty-two tumors arose in the midline, whereas 17 examples were found in the left lateral ventricle and 14 in the right; in 10 cases, the location was not specified. Of those tumors localized in the 4th ventricle, 12 were attached to the floor and 10 to the roof, while there were 20 cases with an unknown site of origin. The average tumor size at diagnosis was 25.2 mm (mean, 23 mm) with a range from 2 mm to 60 mm.

Radiographic features

The imaging features are summarized in Table 2. Of the 22 cases available for imaging, the most common location was the fourth ventricle (55%) followed by the lateral ventricles (45%). Hydrocephalus was present in 94% of all cases and was marked in 69%. Peritumoral edema was seen only in 12.5% of cases. Only one subependymoma showed a fluid or “cystic” area as well and transependymal extension was documented in one case by CT only, these represent less than 5% of cases studied.

On non-contrast CT (NCCT) (11 studies), these tumors showed a slightly low attenuation compared to gray matter in 75% of cases. Characteristic findings are illustrated in Fig. 1. Hyperattenuation in these subependymomas was rare, seen in only 15% of cases. On NCCT, there was no significant difference between a homogeneous and heterogeneous pattern of attenuation. Following intravenous contrast material administration, the majority of tumors enhanced and the degree of enhancement was mild in 36% of cases, moderate in 21% and marked in 14%. Twenty-one percent did not enhance. As on NCCT, there wasn't a significant difference between the homogeneous and heterogeneous patterns on iodine enhanced CT (ECCT).

On MR (12 studies) these tumors (Fig. 2) were heterogeneous in 2/3 (67%) of cases. On T1 weighted images, 6/12 (50%) of subependymomas were isointense compared

Fig. 1 Subependymoma in a 73-year-old woman with a history of emesis and behavioral changes from baseline for 6 months. **(a)** Axial NCCT image shows bilateral enlargement of lateral ventricles due to bilateral masses that are slightly lower in attenuation than brain parenchyma. **(b)** Axial FLAIR weighted MR image shows heterogeneous hyperintensity within the tumors. **(c)** Contrast-enhanced axial T1 weighted MR image shows mild heterogeneous enhancement of the masses. **(d)** Contrast-enhanced coronal T1 weighted MR image shows mild heterogeneous enhancement of the masses. **(e)** Coronal section of brain at the level of the anterior commissure showing a lobulated mass filling bilateral anterior horns of the lateral ventricle

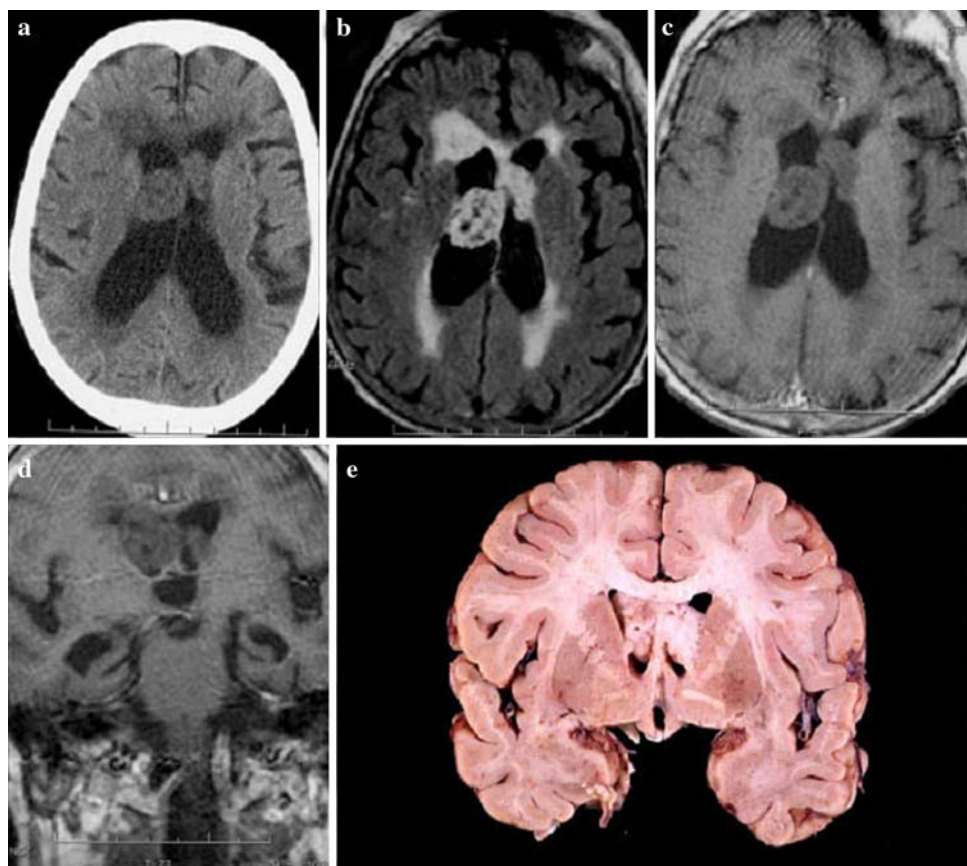
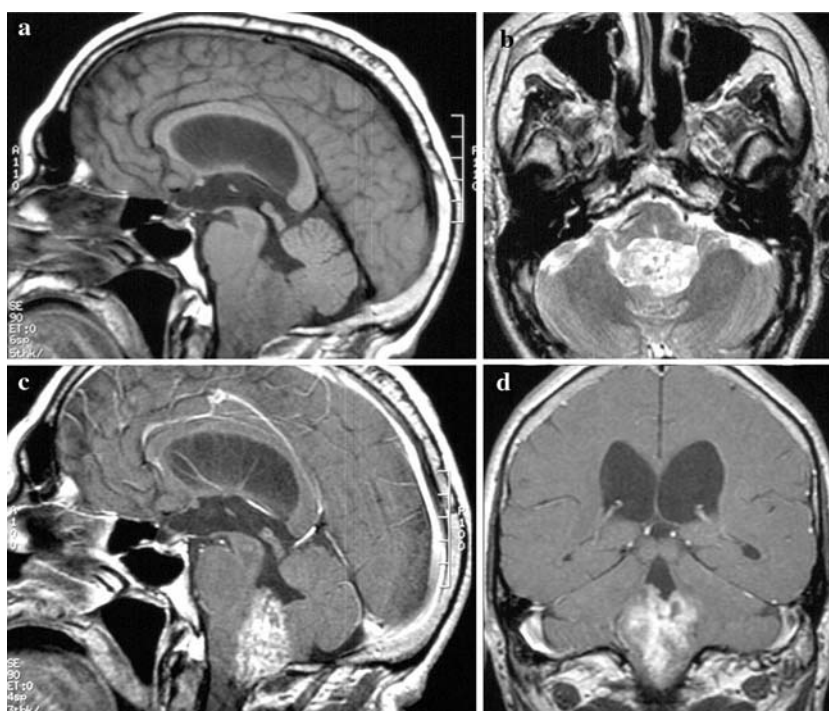


Fig. 2 Subependymoma in a 46-year-old man presented with headache and decreased balance. **(a)** Sagittal T1 weighted MR image shows an isointense fourth ventricular mass with inferior extension through the foramen magnum. **(b)** On an axial T2-weighted MR image, the mass is mildly hyperintense compared with the cerebellum **(c)** On a contrast-enhanced sagittal T1-weighted MR image and **(d)** coronal, the mass shows intense but heterogeneous enhancement



with gray matter and 30% hypointense to gray. Compared to white matter, 80% of cases showed an increased signal. Hemorrhage, identified as hyperintensity on T1-weighted images, was detected only in a single case. On T2 weighted images, 87.5% of cases were hyperintense in comparison with either gray or white matter. On intermediate (proton-density- weighted images, all tumors were hyperintense in comparison with either gray or white matter. The majority (80%) enhanced following gadolinium-based contrast material administration on T2-weighted images.

Pathologic findings

On gross inspection, the tumors presented as firm, smooth-contoured lobulated masses bulging into the ventricular cavity. Although unencapsulated, in all instances the tumor appeared well delineated from the surrounding brain parenchyma. Small punctate or sometimes extensive calcific areas gave tumors, especially those from the posterior fossa, a gritty sensation when cut.

Microscopically, the majority of tumors varied little in appearance: Characteristically, these tumors displayed a distinct nodular pattern imparted by irregular cellular distribution with zones of relatively high nuclear density alternating with a dense fibrillary stroma (Fig. 3). In the cellular zones, the nuclei sometimes radiated around small, capillary caliber blood vessels, forming perivascular pseudorosettes. The overall histopathologic features are tabulated in Table 1. Cyst formation was limited to tumors located in the lateral ventricles, but other features were not related to location.

Overall, 18% (15/83) of subependymomas exhibited a mixed histologic pattern; that is, subependymoma together with another glial tumor. Of these, the most common

Table 1 Histopathologic features of 83 subependymomas

Histologic feature	% cases
Calcification	17
Cystic	23
Necrosis	2
Vascular hyalinization	68
Pleomorphism	23
Mitoses	2
Hemosiderin	8
Mixed	18
Abrupt transition	78

More than one feature may be present in a single tumor

mixture (13/15) was subependymoma and ependymoma. Two tumors contained areas of astrocytoma mixed with subependymoma. The proportion of subependymoma in the mixture varied from 95 percent to as little as 15 percent, and the transition from one tumor type to another could be abrupt (8/15) or indistinct (6/15). Mixed patterns were more likely to be in surgical (14/15) than in autopsy (1/15) material. There are 7 (7/34) mixed examples with known outcome (Table 2).

Not surprisingly, in the cases (14/83) with available GFAP stained sections, all were strongly positive. As assessed by nuclear staining with the Ki-67 antibody, the proliferation index in our cases (9/83) was extremely low, in many cases approaching zero.

Chromosome 22 status

CISH was successfully performed in 8 tumors and the positive controls. The hybridization signals were easily

Fig. 3 Microscopic features of subependymoma (a) Fourth ventricle tumor showing characteristic lobular growth pattern (10×) (b) Microcystic change is often prominent in subependymomas within the lateral ventricles (100×) (c) The presence of two intranuclear signals (arrow) within the majority of neoplastic cells confirms that NF2 deletions were not identified. (CISH, 400×) (d) Mixed subependymoma-ependymoma: the arrows point to the subependymomas component (160×)

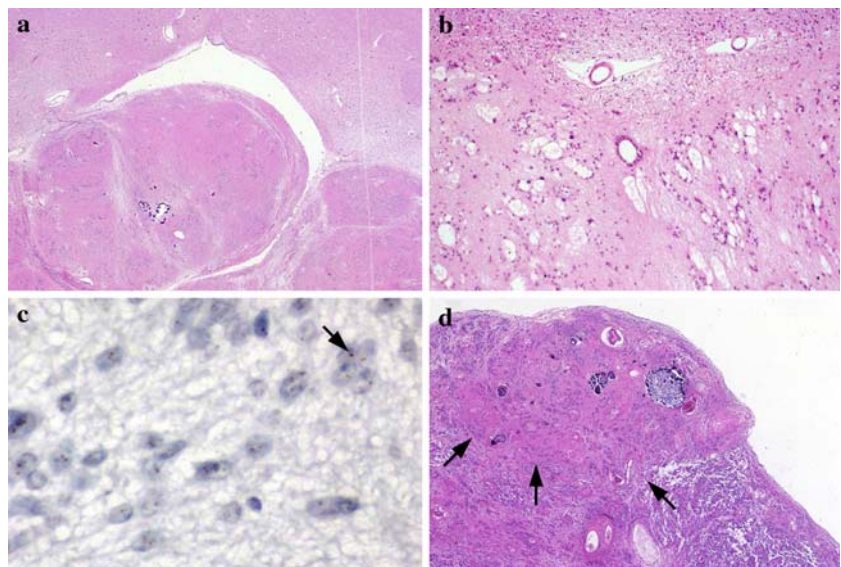


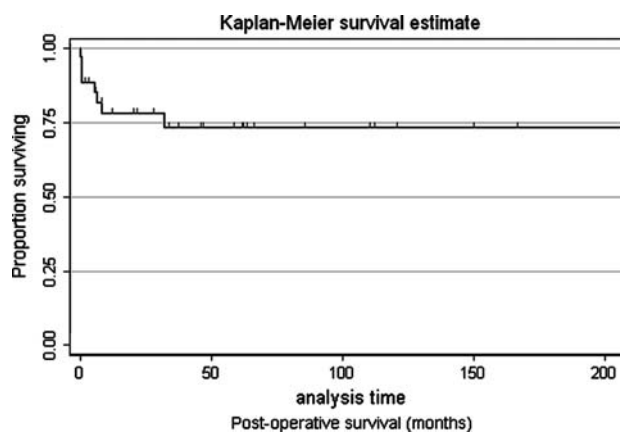
Table 2 Radiographic findings in 22 cases

Hydrocephalus	CT		94%	
	MRI		83%	
Peritumoral edema	CT		12.50%	
	MRI		0%	
NCCT	Attenuation	low	75%	
		iso	10%	
		high	15%	
	pattern	homogeneous	50%	
		heterogeneous	50%	
ECCT	enhancement	no	21%	
		mild	36%	
		moderate	21%	
		marked	14%	
		pattern	homogenous	45%
		heterogeneous	55%	
	T1w MRI	signal intensity*	low	30%
			iso	50%
high			20%	
Enhancement		no	20%	
		mild	20%	
		moderate	0%	
Pattern	homogenous	60%		
	heterogeneous	33%		
T2w MRI	signal intensity*	low	12.50%	
		iso	0%	
		high	87.50%	
PDw MRI	signal intensity*	low	0%	
		iso	0%	
		high	100%	

detected at light microscopy and are illustrated in Fig. 1b. In our group of representative tumors, all were diploid exhibiting two hybridization signals in the neoplastic cells.

Treatment and outcome

Complete follow-up information was available for 34 patients, of whom 26 were alive and 8 dead by the end of the study. Specific details regarding the surgical approach were not available. Average follow-up time for these 34 cases was 48 months (range, 10 days–207 months). Eight deaths were observed (23.5%) during the follow-up period. Six deaths (18%) occurred during the immediate postoperative period and were felt to be related to surgical complications. In the remaining 2 cases, additional details are lacking. Five-year survival percentages were estimated using the Kaplan–Meier method (Fig. 4), and survival curves were compared using the log rank test. Table 3 summarizes the patient and tumor characteristics in these

**Fig. 4** Kaplan–Meier survival curve for 34 patients with subependymoma

34 cases. Age at time of surgery is the only variable found to be significantly associated with survival. Ten patients received adjuvant radiation therapy, but follow-up data was unavailable for one of these patients.

Discussion

In contrast to the largest previous study [24], which reported an overall tumor-related mortality of 51%, analysis of our combined cohort of 34 symptomatic cases revealed a significantly reduced mortality of 23.5%. Although we were unable to obtain specific details regarding the surgical intervention, the more favorable prognosis in our series is likely attributable to advances in diagnostic imaging and microneurosurgical techniques [6].

The current surgical approach to intracranial subependymomas is similar to that of other intraventricular or paraventricular tumors [6]. The exact approach will depend upon the exact location of the lesion, the amount of hydrocephalus that is present, and the comfort and experience of the surgeon. The use of neuronavigation is useful for efficient approach to smaller lesions and to help guide the extent of resection. Meticulous use microneurosurgical technique and operative microscope to enhance maximal safe removal is important in these lesions as with other low grade tumors [6]. The general concept of maximal safe tumor resection and restoration of normal CSF pathway is the ultimate goal of surgery. There may be a role for use of intraoperative MRI to enhance extent of tumor resection in questionable cases; however, in this series there did not appear to be a significant survival difference between gross total and sub total resections. Subtotal resections may be re-operated on if necessary to re-establish CSF flow, or may be monitored with serial imaging. Addition of adjuvant treatment such as radiation needs further evaluation.

Table 3 Five-year survival, by patient and tumor characteristics in 34 cases

	5-year survival			
	Number of cases	Percent	95% confidence interval	<i>P</i> value (log rank test)
Total	34	73.38	53.11–85.95	
<i>Age</i>				0.0042
≤ 50 years	19	93.75	63.23–99.10	
> 50 years	15	46.93	18.07–71.58	
<i>Sex</i>				0.0783
Female	8	100.0	–	
Male	26	64.42	40.19–80.88	
<i>Tumor size</i>				0.8121
≤ 30 mm	18	68.78	39.30–86.08	
> 30 mm	14	76.19	42.09–91.81	
<i>Tumor location</i>				0.5130
4th ventricle	15	72.00	41.15–88.56	
Lateral ventricle	17	80.67	51.12–93.36	
<i>Extent of resection</i>				0.7743
Gross total	18	76.92	49.40–90.70	
Sub total	10	78.75	38.09–94.26	
<i>Postoperative radiation</i>				0.7903
Yes	10	74.07	28.92–93.00	
No/unspecified	24	72.65	48.30–86.91	
<i>Histology</i>				0.6702
Pure	27	74.24	50.63–87.78	
Mixed	7	68.57	21.28–91.21	

The rare intramedullary subependymoma is also surgically treated similar to other intramedullary ependymomas [24]. Standard approach through posterior myelotomy at the point where the lesions most closely approaches the surface is sufficient. This determination is often assisted by using intraoperative ultrasound. The use of neurophysiological monitoring, operative microscope, and microneurosurgical techniques will assist with maximal safe resection [6]. Of particular interest, Shimada described two cases of spinal cord subependymomas, which were histopathologically similar, one of which recurred 9 years after the initial operation [24].

There was no clear evidence in our data that tumor size or location play a significant role in determining clinical behavior. Age alone was found to exert a significant effect on outcome. The conclusion that older patients have a worse prognosis is not surprising, given their greater likelihood to suffer surgical complications due to underlying diseases and other age-related factors. Surprisingly, we were not able to find a significant difference in survival based on extent of resection. Unfortunately, we did not have follow-up data in our patients who received postoperative radiation, which precluded an analysis of this therapy. Maiuri found a similar favorable long-term outcome in cases that had a subtotal resection [14]. Of further

interest, unlike the previous study, which concluded that mixed histology was associated with an 80% mortality rate, we did not find a correlation between survival and the mixed examples in our cases. Possible explanations for this observation include the few cases of mixed histology with follow-up (7/34), and the low-grade histology, especially the minimal mitotic activity in all our examples.

The molecular profile of ependymal neoplasms is poorly characterized and warrants further investigation. Ependymomas may occur sporadically or in association with neurofibromatosis 2 (NF2), an autosomal dominant disorder, which predisposes to multiple schwannomas, meningiomas and spinal ependymomas, in particular [4, 26]. The most frequent genetic alteration has been the loss of the Protein 4.1 family member, NF2, predominantly in spinal ependymomas [18]. In a study of 21 symptomatic tumors, flow cytometry revealed a diploid pattern in 12 patients, tetraploidy in two and aneuploidy in one [13]. Even less has been published about the genetics of subependymomas. A cytogenetic study of subependymomas by Dal Cin et al. failed to identify characteristic aberrations [3]. Another molecular genetic analysis that included 2 cases of subependymoma did not detect allelic mutations on chromosomes 10q and 22q or point mutations of the *NF2* and *PTEN* tumor suppressor genes [5]. CISH methods for

in situ hybridization enable the determination of chromosome 22 status using routine light microscopy on routinely processed paraffin sections [15, 21]. In selected examples in our series, NF2 deletions were not identified by CISH. Although not definitive, given the small sample number, our results point to alternative molecular pathways in the pathogenesis of subependymoma.

Although there is no convincing evidence that the predisposition to develop subependymomas is inherited, Ryken et al. [20] describe the first reported occurrence of fourth ventricular subependymoma in a father and son. With the exception of a single patient with NF1, there were no other cases in our series that appeared to be related to inherited syndromes.

The imaging features in our 22 examples with minor exceptions confirm previous observations. Most subependymomas are smaller than 2 cm in diameter; however, symptomatic subependymomas are usually larger, averaging about 4 cm in greatest dimension [2, 5, 17, 25]. The typical appearance of a subependymoma on CT is a well-circumscribed, lobulated intraventricular mass that is predominantly slightly lower on attenuation compared with gray matter, in about 75% of cases. Hydrocephalus is present in 94% of cases—in symptomatic series [2]. Calcification is seen in half of cases, although dense calcification is not common [5, 17, 27]. Hemorrhage [11, 17, 25] and cystic degeneration (18%) are frequent in the literature [2, 17], although the former is rare in our series. Occasionally, subependymomas may produce peritumoral edema on cross-sectional images [5, 17]. Following intravenous contrast material administration, the majority of subependymoma showed at least some enhancement, mild in 36% of cases, moderate in 21% and marked in 14%. Only 21% of subependymomas do not enhance. As well as on non-contrast enhanced CT (NCCT), there is no significant difference between homogeneous and heterogeneous lesion pattern on contrast-enhanced CT (CECT) [12].

In an attempt to differentiate subependymomas from ependymomas with imaging studies alone, it should be emphasized that subependymomas tend to be intraventricular, whereas ependymomas tend to be paraventricular [12]. Hyperattenuation compared with the brain parenchyma, enhancement, calcification, and cyst formation are also more commonly seen in ependymomas than in subependymomas, occurring in about one-half of cases. However, none of these features is particularly distinctive. The differentiation between these two tumors is even less apparent when they arise near the fourth ventricle [5, 9, 12].

On T1 weighted MR, 50% of subependymomas are isointense compared with gray matter and 30% hypointense. Comparing with white matter, 80% of subependymomas are hypointense. On T2 weighted images, the majority of

subependymomas (over 87%) were hyperintense compared with both gray and white matter [2, 7, 9].

Heterogeneity is typical and is seen in up to 67% of cases. Cyst like fluid areas interspersed within the mass may be noted. When hemorrhage is present, characteristic signal intensity from hemoglobin by-products is noted [25]. Extension of a subependymoma beyond the ventricular margins is rare (5, 9).

Enhancement is quite variable on contrast-enhanced images [2, 25]. They may not enhance, enhance minimally, or show intense enhancement after the intravenous administration of a contrast agent [9, 17]. Even when intense enhancement is seen, it is usually heterogeneous. In our series of 12 cases studied by MR, most tumors were isointense or hypointense to gray matter on T1 images; and, most tumors were hyperintense on T2 sequences. The majority of the tumors showed contrast enhancement. These results are similar to the case series reported from Utah and probably reflect increased water within the neoplasms. The majority of tumors showed contrast enhancement—also consistent with the Utah group. These features may be helpful in distinguishing subependymomas from ependymomas, since the latter frequently have intense enhancement and extraventricular extension [9, 17].

Conclusions

Subependymomas are benign neoplasms for which current surgical techniques result in an excellent long-term clinical outcome. Neuroimaging features are nonspecific, but there are subtle clues that may aid the clinician to consider this entity. In our limited sample, subependymomas do not appear to be associated with NF2 mutations that are found in other ependymal neoplasms.

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